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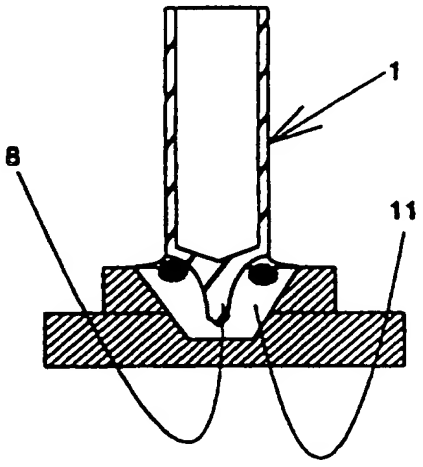
(54) Title: MAGNETIC PARTICLE TRANSFER DEVICE

(57) Abstract

The invention relates to a means for separating magnetic particles from a composition and for transferring them into a liquid in a vessel. The means comprises an elongated body (1) that comprises a device which can be used to align the longitudinal magnetic field of a protective cover with the lower end of the cover and eliminate the effect of the field from the lower end, and a tip part (8) at the lower end of the body, which is tapered in a concave manner. The means is especially well-adapted for transferring particles to very small vessels. The invention can be used in different applications, especially in the fields of biotechnology, biochemistry, and biomedicine.



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MAGNETIC PARTICLE TRANSFER DEVICE

TECHNICAL FIELD

The invention relates to the separation of magnetic particles from a composition containing them and the transferring of them to a liquid. The invention can be used in different applications, especially in the fields of biotechnology, biochemistry, and biomedicine.

Magnetic microparticles are used as a solid phase in various applications to bind biomaterial. One advantage of microparticles is the large area of the solid phase and short diffusion lengths. The size of microparticles is generally 0.05 - 10 μm and they are available in different materials and already activated for many applications. Magnetic particles can be moved by using a magnetic field.

The separation methods of magnetic particles presently used include settling a reaction vessel in a magnetic field so that particles are accumulated into a so-called pellet at the bottom of the vessel. Thereafter, the liquid which is free from particles is decanted or removed by aspiration. However, the removal of the liquid from the vessel must be carried out very carefully so as not to remove the particles at the same time.

Publication EP-140787 (corresponding publication US-4649116) proposes a method by which magnetic particles are separated from a liquid by using a magnetic rod which is pushed into the liquid. The particles are pulled off the rod by using a stronger magnet.

Publication WO-87/05536 suggests a device for separating magnetic particles which contains a rod movable in a vertical bore and provided with a magnet at the lower end thereof. The device is introduced into a liquid containing particles with the magnet in a lower position, whereby particles are collected at the end of the rod. When the magnet is allowed in an upper position, particles can be detached from the rod. In this way, particles can be collected and transferred from one liquid to another. The tip of the device is shaped like a cylinder thinner than the arm.

Publication WO-94/18565 proposes an assay method in which magnetic particles are separated from a liquid by using a rod comprising a conical tip and containing a movable magnet. In the application according to Figs. 2, the rod comprises a

concave and tapering tip part but particles are collected above this tip part, as shown in Fig. 2b.

However, the proposed separation devices and methods of magnetic particles are not very well-adapted to applications in which particles have to be transferred into very small vessels. The known devices are not very well-adapted for those applications either in which particles are collected from a large volume with respect to the means of separation.

DESCRIPTION OF THE INVENTION

General Description

Now, a transfer device according to Claim 1 has been invented. Some preferred applications of the invention are presented in the other Claims.

The device according to the invention comprises an elongated body comprising a means which can be used to align a magnetic field in the direction of the body to the tip of the body when particles are to be collected on the tip and eliminate the effect of this magnetic field when particles are to be released from the tip. Such a magnetic field is especially advantageous in such cases where particles are first collected in some other way, e.g., from a concentration of particles provided on the wall of a test tube. The tip part of the body is tapered and comprises a concave surface. The height of the tip part is slightly higher than the height of the vessel in which the particles are released. The width of the tip part at the upper part thereof is slightly smaller than the diameter of the vessel. When the tip is pushed into the vessel, the surface of the liquid in it rises along the surface of the tip under the influence of surface tension. The edge of the moving liquid surface wipes the particles off the tip and into the liquid. The detachment can be improved by moving the rod. Correspondingly, when the tip is raised from the well, the surface of the liquid moves as an integral film towards the end of the tip. In this way, the liquid and particles along with it are completely detached from the tip.

The cross-section of the tip part is preferably circular but, in principle, any other shape can be considered. A wedge-like form could be for tray-like vessels of a rectangular shape, for example.

The tip is preferably sharp. Liquid can be detached from a sharp tip in the most complete way possible. Furthermore, the sharp tip facilitates the placing of the tip into a vessel when the tip will rest at the bottom of the vessel.

The body preferably comprises an elongated protective cover which comprises a movable rod provided with one rod magnet in the longitudinal direction of the protective cover. The proportion of the length of the rod magnet to its thickness is preferably at least about 2:1, preferably about 3:1, and most preferably about 12:1. Both the strength and the gradient of the magnetic field thus provided are the strongest at the end of the rod, and when the magnet is in the lower position, particles are accumulated from the composition into the tip part of the protective cover in a concentrated manner.

The rod magnet is preferably comprised of a permanent magnet and a ferromagnetic arm which comprises its extension.

The rod magnet is preferably sufficiently long so that when collecting particles, the upper end of its dipole always remains above the surface of the composition. Should particles be collected from a column higher than the dipole, it must be seen to that particles are collected to the tip first from the upper part of the column so that the upper end of the dipole is above the particles the whole time. When collecting particles from very small volumes, the magnet is preferably completely above the surface. Only the magnetic field extends to the compound and the lower flange of the tip gets completely wet when the tip is placed against the bottom of the vessel.

When the magnet is provided with a ferromagnetic arm, the magnet and the magnetised arm together serve as a long rod magnet. The arm fades out the gradient of the upper pole of the field, whereupon the upper pole does not carry out collection of particles. In this way, the long rod magnet can be manufactured at a lower cost. However, even with the ferromagnetic arm, it is preferable to use a relatively long magnet (e.g., with a length of about 2...10 times the diameter). The length of the magnet is preferably selected so that a maximum internal and permanent field strength is provided for the magnet in question.

The cross-section of the rod magnet can be circular or rectangular, for example. With respect to both the manufacture and the use, the circular shape is preferable. For instance, in this case, the twisting of the magnet around its axis has no

influence. In principle, the rod can also be provided with a curved shape to simplify the moving mechanism.

The protective cover on top of the rod can have various shapes according to the use. Normally, the circular shape is the most advantageous with respect to both the manufacture and use. To increase strength, the protective cover can be made conical, which facilitates the manufacture of the cover by injection moulding. The cover is suitably manufactured from polypropylene, for example.

The junction of the magnet and the arm is preferably made so that the arm and the magnet are within one another for a short length. In this way, the formation of strong gradients on the junction, which perhaps collect particles, is avoided.

The best way to separate the particles from the liquid is to first concentrate them at one point in the vessel from where they are then collected by using the rod. The concentration can be effected by letting the particles settle under the effect of gravitation, by using a centrifugation, or by pulling the particles onto the wall of the vessel by using a magnetic field. The use of a magnet is the best way in most cases.

The invention is best applied to particles of about 1 - 10 µm.

Drawings

Some advantageous applications of the invention are described by way of example in the following. The drawings of the description comprise:

Fig. 1 which presents one separation means according to the invention,
Fig. 2 which presents the use of the means of Fig. 1 for collecting particles from a suspension,
Fig. 3 which presents the use of the means of Fig. 1 to release the collected particles; and
Fig. 4 which presents an enlarged detail of the tip portion of the separation part according to Fig. 1 when releasing particles into a vessel.

Examples

The separating rod according to Fig. 1 comprises elongated protective cover 1 which is provided with bore 2. The lower ends of the protective cover and the bore are slightly tapered. The upper end of the body comprises gripping flange 3.

There is loose magnetic rod 4 in bore 2. The rod is provided with vertical rod magnet 5 at the lower end thereof and above that, with ferromagnetic arm 6 as an extension of the magnet. The end of the arm is provided with gripping nub 7.

The lower end of the cover is provided with tapered and sharp tip 8 with a concave surface. The length of the tip approximately corresponds to the width of the lower end of the cover.

Fig. 2 presents the collecting of particles from the wall of the test tube on which they were first pulled by using a magnet to form vertical strip 9. By sweeping along the strip with the tip of the rod, particles are made to adhere on the tip of protective cover 1 of the rod to form circular mass 10. When magnet 5 is kept in the lower end of bore 2, particles remain attached to the tip. When particles are to be released, the magnetic rod is lifted up.

Tip 8 is especially well-adapted for transferring particles into a very small vessel, such as well 11 of a so-called HLA plate (Fig. 3).

Fig. 4 is an enlarged drawing of tip 8 in well 11. The tip is slightly longer than the height of the well. When the tip is pushed into the well, the surface of the liquid in it raises upwards along the surface of the tip under the effect of surface tension. The edge of the moving surface of the liquid sweeps the particles off the tip and into the liquid. The detachment can be improved by moving the rod. Correspondingly, when the tip is lifted out of the well, the surface of the liquid moves as an integral film towards the sharp end of the tip. In this way, the liquid and the particles along with it are completely detached from the tip.

When a conical well according to Fig. 4 is used, the minimum of the gap between the liquid and the tip is between the edge of the lower surface and the upper edge of the well. The liquid tries to minimise its area under the influence of surface tension, whereby the liquid settles evenly around the tip, covering the whole lower flange. The search for the minimum gap size is effected very quickly, whereby the stream of liquid sweeps the particles off the surface of the tip. When the tip is slowly detached from the liquid, the liquid seeks its minimum area every moment and the surface tends to remain integral. Finally, the end of the tip is detached from the liquid and the tip is removed from the liquid in a nearly dry state.

When releasing particles, the protective cover can be supported at its tip at the bottom of the vessel.

The proportion of the length of magnet 5 to its thickness is about 10:1 and the proportion of the length of the arm to the length of the magnet is about 5:1. The arm is slightly thicker than the magnet and the upper end of the magnet is embedded inside the lower end of the arm for a length of about twice its thickness.

CLAIMS

1. A means for separating magnetic particles from a composition containing them and for transferring them into a liquid in a vessel, **characterised** in comprising:
- an elongated body (1; 1') with an upperend and a lower ends,
- a concavely tapered tip part (8) at the lower end of the body, and
- the body comprising a device which can be used to align a longitudinal magnetic field to the tip part to collect particles to it, and to eliminate the effect of the field from the tip part to release the particles from it.

2. A means according to Claim 1, **characterised** in that the cross-section of the tip part (8) is circular.

3. A means according to Claim 1 or 2, **characterised** in that the end of the tip part (8) is sharp.

4. A means according to any of Claims 1-3, **characterised** in that the lower end of the body (1; 1') is provided with a magnet (5) in the longitudinal direction of the body.

5. A means according to Claim 4, **characterised** in that the body comprises a magnetic rod (4) in the longitudinal direction of the body, the proportion of the length of the rod to its thickness being at least about 2:1, preferably about 3:1.

6. A means according to Claim 5, **characterised** in that the magnetic rod (4) comprises a magnet (5) at the lower end thereof and a ferromagnetic arm (6) is attached to the upper end of the rod.

7. A means according to Claim 6, **characterised** in that the proportion of the length of the magnetic rod (4) to its thickness is at least about 12:1.

8. A means according to Claim 6 or 7, **characterised** in that the upper end of the magnet (5) and the lower end of the arm (6) are inside one another.

9. A method for separating magnetic particles from a composition containing them and for transferring them into a liquid in a vessel, **characterised** in that a means is used for the transfer, which comprises:
- an elongated body (1; 1') with an upperend and a lower ends,

- a concavely tapered tip part (8) at the lower end of the body, and
- the body comprising a device which can be used to align a longitudinal magnetic field to the tip part to collect particles to it, and to eliminate the effect of the field from the tip part to release the particles from it.

10. A method according to Claim 9, **characterised** in that the transfer means comprises a magnet which is completely above the surface of the compound when particles are being collected.

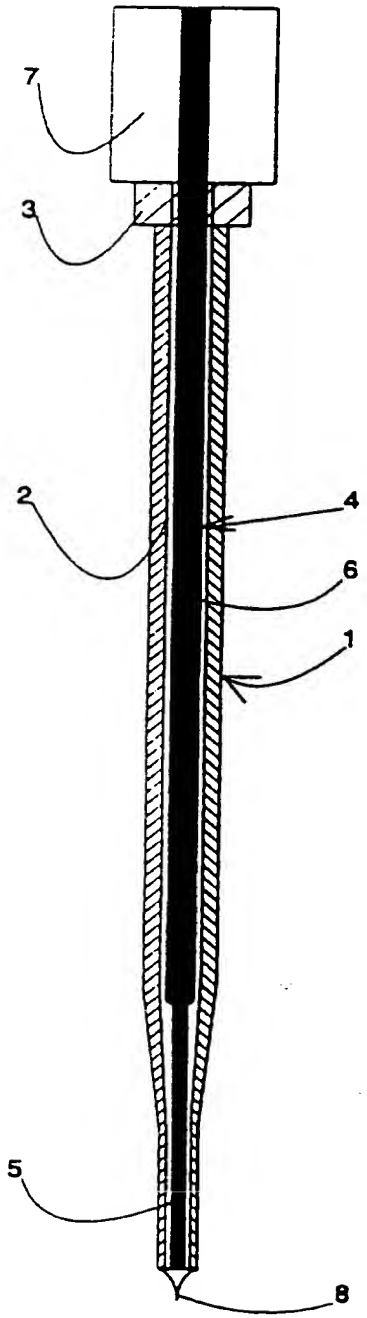

Fig. 1

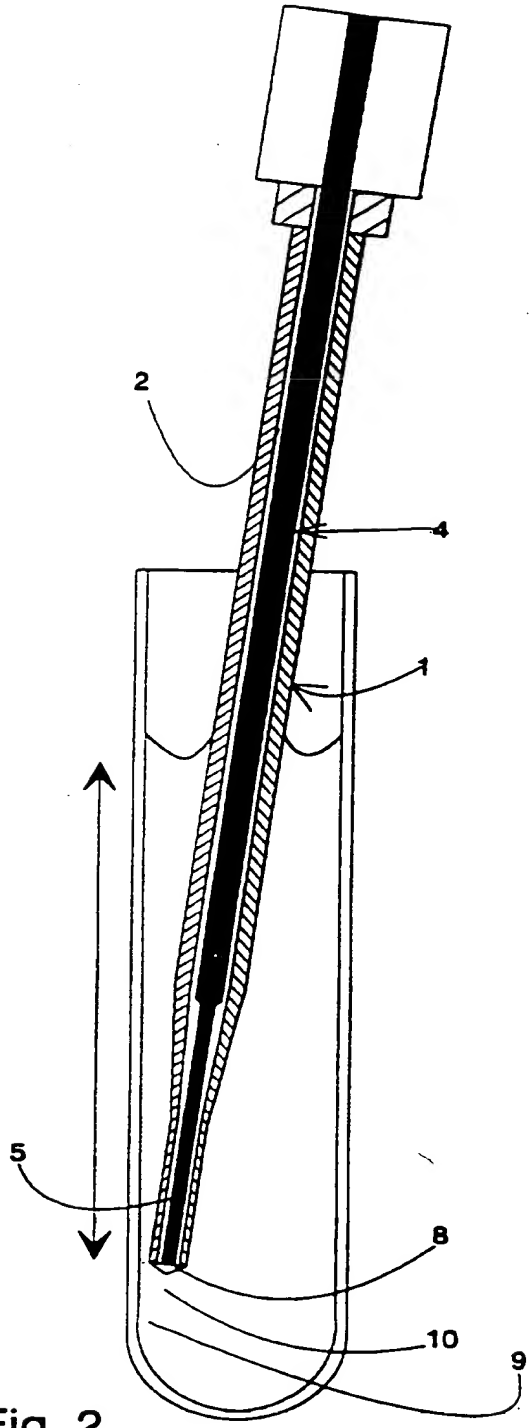

Fig. 2

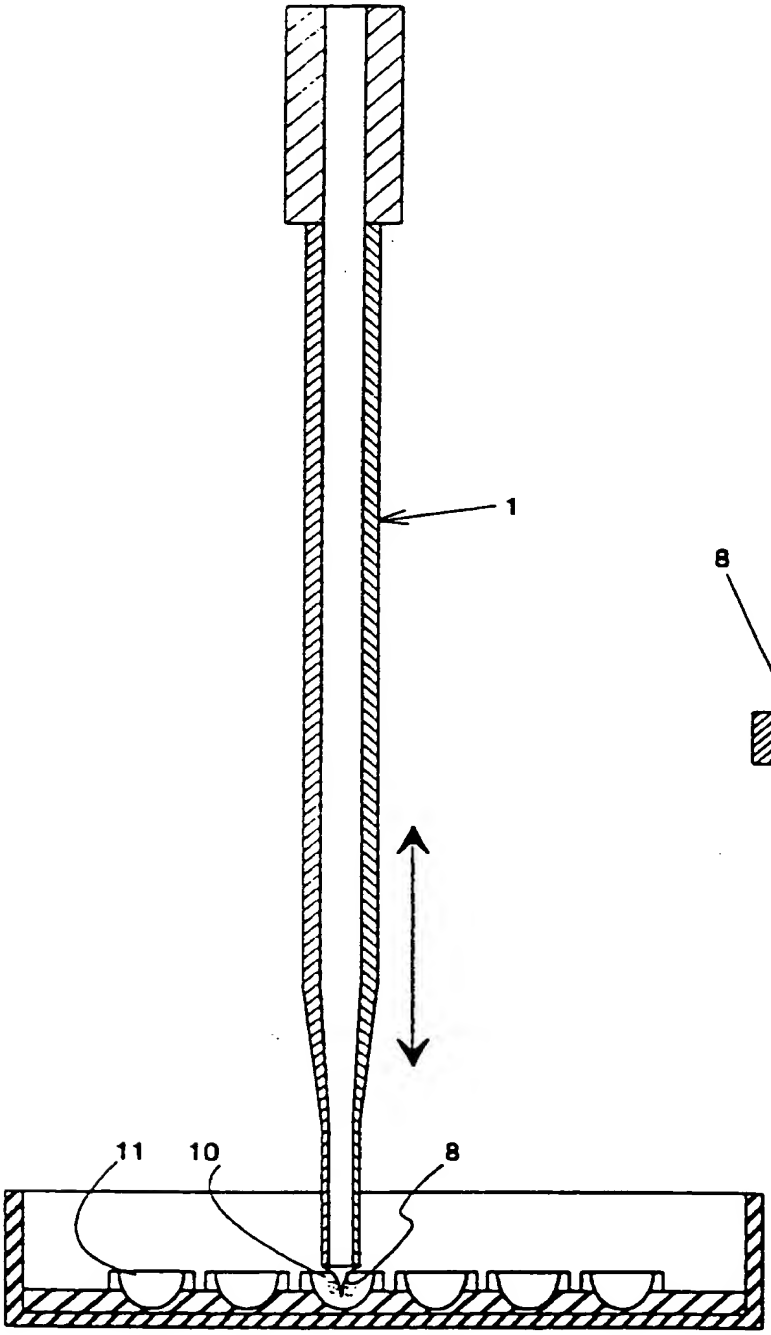

Fig. 3

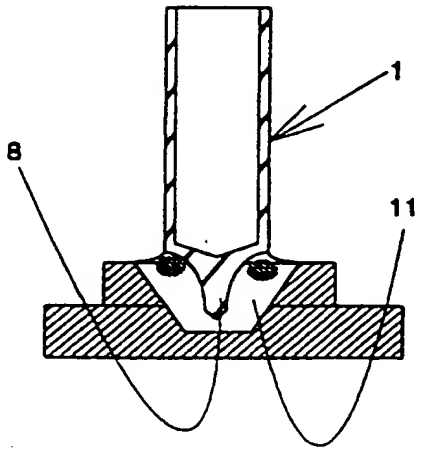

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 95/00578

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: G01N 33/543, G01N 33/553, B03C 1/28
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: G01N, B03C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9418565 A1 (LABSYSTEMS OY), 18 August 1994 (18.08.94), see figures 2a and 2b ---	1-9
A	WO 8705536 A1 (CARBOMATRIX AB), 24 Sept 1987 (24.09.87) ---	1
A	US 5466574 A (PAUL A. LIBERTI ET AL), 14 November 1995 (14.11.95), column 5, line 62 - line 67 --- --------	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
14 February 1996	01.03.96
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INTERNATIONAL SEARCH REPORT

Information on patent family members

05/01/96

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9418565	18/08/94	NONE	
WO-A1- 8705536	24/09/87	AU-A- 7127787	09/10/87
		SE-A- 8601143	13/09/87
US-A- 5466574	14/11/95	WO-A- 9415696	21/07/94
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